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(71) Applicant: **TANABE SEIYAKU CO., LTD.**

**Chuo-ku Osaka (JP)**

(72) Inventors:

- **Hatano, Harumi**  
**Amagasaki-shi, Hyogo-ken (JP)**

- **Ito, Takahiro**

**Yao-shi, Osaka-fu (JP)**

- **Ishibashi, Takashi**

**Sakai-shi, Osaka-fu (JP)**

- **Yoshino, Hiroyuki**

**Suita-shi, Osaka-fu (JP)**

- **Mizobe, Masakazu**

**Takatsuki-shi, Osaka-fu (JP)**

(74) Representative: **Koch, Gustave et al**

**Cabinet PLASSERAUD**

**84, rue d'Amsterdam**

**75440 Paris Cédex 09 (FR)**

(54) **Pharmaceutical preparation in form of coated capsule releasable at lower part of digestive tract**

(57) A pharmaceutical preparation in the form of a coated capsule which can release contents of a capsule at a lower part of the digestive tract comprising (a) a hard capsule containing at least an acidic substance, (b) a polymer film soluble at low pH which is formed on a surface of said hard capsule, and (c) an enteric coating film which is formed on a surface of said polymer film soluble at low pH. According to the pharmaceutical

preparation of the present invention, any kind of a medicament can be delivered to any desired site between the upper part of the small intestine and the lower part of the large intestine in the digestive tract by controlling the amount of polymer(s) used for the polymer film soluble at low pH and/or by selecting the kind of the polymer film soluble at low pH and/or the acidic substance without any complicated requirements for each medication.

## Description

The present invention relates to a pharmaceutical preparation which can release contents of a capsule at a lower part of the digestive tract and more particularly to a pharmaceutical preparation in the form of a coated capsule by which contents of a capsule can be selectively delivered to a desired site, e.g. the large intestine, and quickly released thereat.

Selective delivery of a medicament to the large intestine has been desired in drug therapies, for instance, a local therapy for inflammatory disease in the digestive tract such as ulcerative colitis or Crohn's disease, or an oral administrative therapy with a medicament of a peptide which is apt to be decomposed chemically or enzymatically in the digestive tract, with a medicament of which the absorption site is limited, or with other medicament.

In order to efficiently realize the site-selective delivery of a medicament to the large intestine, it is necessary to design a pharmaceutical preparation taking into account the physical and physiological environment in the human digestive tract and the residence time of the pharmaceutical preparation in the digestive tract. With respect to the physical and physiological environment in the digestive tract, it is recognized that the value of pH in the stomach is usually 1.8 to 4.5 in a healthy human and that the value of pH in the intestines is 6.5 to 7.5. According to the results of the widespread research of Davis et al., the residence time of a pharmaceutical preparation in the human stomach is 0.5 to 10 hours. Further not only is the inter-individual variation of the residence time large, but also the residence time is considerably influenced, for example, by feeding, the size of the pharmaceutical preparation to be administered and the like. On the other hand, the passage time of a pharmaceutical preparation through the small intestine is generally recognized to be  $3 \pm 1$  hours and the inter- and intra-individual variation is relatively small (Journal of Controlled Release, 2, 27-38 (1985)).

With respect to a method by which a medicament can be selectively released at the large intestine, hitherto various researches have been done. There have been proposed a pharmaceutical preparation which is obtained by coating a sustained release pharmaceutical preparation with an enteric coating (Annals of the New York Academy of Science, 618, 428-440 (1991)), a pharmaceutical preparation utilizing a technique for controlling the starting time of the release (Chemical & Pharmaceutical Bulletin, 40, 3036-3041 (1992), European Patent Publication No. 0425699 and Japanese Unexamined Patent Publication No. 256166/1994), a pharmaceutical preparation in the form of tablet which is obtained by coating insulin with an azopolymer soluble at the large intestine (Saffran et al, Science, 233, 1081-1084 (1986)) and the like, as well as pharmaceutical preparations using known techniques such as an enteric pharmaceutical preparation and a sustained release pharmaceutical preparation.

However, every conventional method has a problem such as insufficient site-selectivity, poor practicality due to peculiarity of the material to be used or complicated process for manufacturing a preparation.

For instance, as the enteric pharmaceutical preparation starts to release a medicament abruptly at the upper part of the small intestine, a selective delivery of the medicament can not be achieved.

When using the sustained release pharmaceutical preparation, a considerable amount of a medicament is released while the pharmaceutical preparation stays in the stomach and passes through the small intestine because the medicament is continuously released.

Furthermore, attempts have been made to suppress the release of a medicament in the stomach by coating a sustained release pharmaceutical preparation with an enteric coating. However, the problem that the medicament is released during the passage of the pharmaceutical preparation through the small intestine, has not entirely been solved by the above-mentioned enteric-coated sustained release pharmaceutical preparation.

The conventional pharmaceutical coated preparation requires optimization of, for example, a combination of a medicament and a coating agent, a coating amount, a kind of a solvent for a coating liquid, a spraying condition, a drying condition and the like, for every medicament to be used. In the case of a medicament which is easily decomposed by heating or by a solvent to be used, the optimization requires much labor.

Furthermore, there are some cases where the obtained optimum conditions are not always applicable to another medicament, in fact, the cases where the conditions are not applicable are numerous compared with cases where applicable. Therefore, it is hard to say that the conventional pharmaceutical preparation is excellent in a wide use.

Additionally, before coating, the conventional pharmaceutical coated preparation essentially requires processes such as granulation process, shieving process and tableting process. Thus, it takes more time, labor and cost.

An object of the invention is to provide a pharmaceutical preparation which is excellent in a site-selective delivery. In particular the object of the invention is to provide a pharmaceutical preparation whereby medicaments, pharmaceutical preparations, functional substances or the like contained in a hard capsule can be delivered to any desired site of the lower part of the digestive tract.

A still further object of the invention is to provide a pharmaceutical preparation in the form of a coated capsule wherein any kind of medicaments etc. can be commonly or widely used without a special formulation.

These and the other objects of the present invention will become apparent from the description hereinafter.

It has now been found that (i) a hard capsule containing an acidic substance which is firstly coated with a substance

soluble at low pH and further coated with an enteric substance, can quickly release contents of the hard capsule at any desired site between the upper part of the small intestine and the lower part of the large intestine according to the kind of the acidic substance and the kind of and the amount of the substance soluble at low pH, and (ii) only if using such a capsule, there can be obtained a pharmaceutical preparation whereby any kind of a medicament, a pharmaceutical preparation, a functional substance or the like can be delivered and quickly released at any desired site between the upper part of the small intestine and the lower part of the large intestine in the digestive tract.

In accordance with the present invention, there is provided a pharmaceutical preparation in the form of a coated capsule which can release contents of a capsule at a lower part of the digestive tract comprising (a) a hard capsule, containing at least an acidic substance, (b) a polymer film soluble at low pH which is formed on a surface of said hard capsule, and (c) an enteric coating film which is formed on a surface of said polymer film soluble at low pH.

The pharmaceutical preparation of the present invention relates to a hard capsule for delivering the contents to the lower part of the digestive tract. That is, the pharmaceutical preparation of the present invention has the following characteristics: When a pharmaceutical preparation stays in the stomach, an enteric coating film protects the pharmaceutical preparation. Successively when the preparation transits from the stomach to the upper part of the small intestine, the enteric coating film dissolves and starts to disappear. Then, the digestive juice gradually penetrates through a low pH-soluble polymer film and a hard capsule to enter the hard capsule, and thereby an acidic substance is dissolved. The solution having low pH which is produced by the dissolution of the acidic substance, dissolves the hard capsule and the low pH-soluble polymer film, resulting in disappearance thereof. Then, the contents of the hard capsule such as medicaments, pharmaceutical preparations and functional substances are quickly released.

Accordingly, the releasing rate of the contents of the hard capsule does not substantially vary with the kind of a hard capsule, the kind or amount of polymer(s) used for a low pH-soluble polymer film or the kind of an acidic substance, and it takes about 1 hour after the start of release to release 80 % of the contents of the hard capsule.

The hard capsule in the pharmaceutical preparation of the present invention is quickly dissolved by a solution having low pH which is produced by the dissolution of the acidic substance. Therefore, the pharmaceutical preparation of the present invention has the characteristic that the lag-time, the time period from the discharge of the pharmaceutical preparation from the stomach till the contents of the hard capsule start to be released, can be controlled to any length by selecting the kind and/or amount of polymer(s) used for a low pH-soluble polymer film and/or the kind of the acidic substance.

Thus, the pharmaceutical preparation of the present invention has an advantage that the contents of the hard capsule can be released quickly and at any desired site of the lower part of the digestive tract.

In addition, a conventional pharmaceutical preparation soluble at the lower part of the digestive tract can be obtained only after the complicated determination of conditions taking into account various processes such as granulation and tableting, protection of a medicament in the stomach and the upper part of the small intestine, the disintegration property in the large intestine, loss of a medicament during preparing a pharmaceutical preparation and the like.

However, the pharmaceutical preparation of the present invention has remarkable advantage that there is no need of the complicated determination of conditions. Namely, according to the present invention, it is not required to determine conditions for the purpose of e.g. protection of a medicament etc. in the process of preparing a pharmaceutical preparation after a medicament etc. is filled into a hard capsule because the medicament etc. to be delivered to the lower part of the digestive tract is filled into a hard capsule.

Fig. 1 shows a sectional view of an embodiment of the pharmaceutical preparation of the present invention.

Fig. 2 shows a sectional view of another embodiment of the pharmaceutical preparation of the present invention wherein a sealing means is provided around the joint of the body and the cap of the hard capsule.

Fig. 3 shows a sectional view of another embodiment of the pharmaceutical preparation of the present invention wherein an intermediate layer is provided between the polymer film soluble at low pH and the enteric coating film.

Fig. 4 shows a perspective view of a hard capsule with a sealing means around the joint thereof.

Fig. 5 is a graph showing the result of the dissolution test with the JP 1st-Fluid and the JP 2nd-Fluid as to a pharmaceutical preparation of the present invention in Experimental Example 1. The term "JP" means the 12th Japanese Pharmacopoeia.

Fig. 6 is a graph showing the change of the concentration of a medicament in the plasma in the case that the pharmaceutical preparation of the present invention was administered to dogs in Experimental Example 1.

Fig. 7 is a graph showing the results of the dissolution test with the JP 2nd-Fluid as to preparations in the form of a capsule coated with Eudragit E100 which are different in the coating amount of Eudragit E100, in Experimental Example 2.

Fig. 8 is a graph showing relationship between the coating amount of Eudragit E100 and the lag-time.

Fig. 9 is a graph showing the results of the dissolution test with the JP 2nd-Fluid as to preparations in the form of a capsule coated with Eudragit E100 which are different in the kind of an acidic substance, in Experimental Example 3.

Fig. 10 is a graph showing the results of the dissolution test with the JP 2nd-Fluid as to pharmaceutical preparations of the present invention which are different in the amount of succinic acid, in Experimental Example 4.

Fig. 11 is a graph showing the results of the dissolution test with the JP 2nd-Fluid as to pharmaceutical preparations of the present invention wherein a sealing means is provided, in Experimental Example 5.

In the present invention, the term "lower part of the digestive tract" means a part from the duodenum as the upper part of the small intestine, via the jejunum, the ileum, the cecum, the ascending colon, the transverse colon, the descending colon and the sigmoid colon, to the rectum.

According to the pharmaceutical preparation of the present invention, contents of a capsule such as a medicament, a pharmaceutical preparation or a functional substance can be selectively released at any desired site of the lower part of the digestive tract as mentioned above. In order to effectively exhibit the characteristic of the present invention, preferably contents of a capsule are released at any desired site between the jejunum and the rectum, more preferably at any desired site between the ileum and the rectum, much more preferably at any desired site of the large intestine between the cecum (the ostium ileocecale) and the rectum. Most preferably, contents of a capsule are released at any desired site of the ascending colon, the transverse colon, the descending colon or the sigmoid colon.

With respect to the hard capsule used in the present invention, any type of hard capsule suitable for oral administration can be used without any limitation, and preferably a commercially available hard capsule is used in view of simplification of the preparation process. Examples of the hard capsule are, for instance, a gelatin capsule such as CONI-SNAP capsule (trade name, commercially available from CAPSUGEL AG, Japan), a corn starch capsule such as CAPILL (trade name, commercially available from Warner-Lambert Company, U. S. A.), a hydroxypropylmethylcellulose capsule such as HPMC capsule (trade name, commercially available from Japan ELANCO CO. LTD., Japan) and the like. Among these, a gelatin capsule and a hydroxypropylmethylcellulose capsule are preferable, and a gelatin capsule is more preferable from a view point of its good dissolution pattern.

The hard capsule in the present invention may be in various types.

A size of the hard capsule is not particularly limited. Preferable capsules have a size of Size No. 2, No. 3 and No. 4 described in the 12th Japanese Pharmacopoeia (hereinafter also referred to as JP XII) in view of handling.

The acidic substance to be contained in the hard capsule used in the present invention is a solid substance of which aqueous solution has pH value of at most 5. The form of the acidic substance is not particularly limited and the acidic substance in various forms such as crystal, powder and granule can be used.

Examples of the acidic substance are, for instance, an organic acid such as succinic acid, maleic acid, tartaric acid, citric acid, fumaric acid or malic acid and an inorganic acid such as boric acid. These acidic substances may be used alone or in the combination of one or more kinds thereof. A preferable acidic substance is an organic acid such as succinic acid, maleic acid, tartaric acid, citric acid, fumaric acid or malic acid, and particularly succinic acid is preferable, due to its good physical and chemical stability, etc.

An acidic substance to be contained in a hard capsule can be a medicament if the medicament is acidic.

The amount of the acidic substance to be contained in the hard capsule is not particularly limited and may be an enough amount to dissolve the polymer film soluble at low pH (hereinafter also referred to as "low pH-soluble polymer film") which is formed around the hard capsule. The optimum amount of the acidic substance can be easily determined by carrying out the dissolution test. The term "low pH" means pH ranging from pH 1 to pH 5, preferably from pH 1 to pH 3.

The polymer soluble at low pH used for the low pH-soluble polymer film in the pharmaceutical preparation of the present invention can be a film-formable polymeric substance which is soluble at the acidic range of from pH 1 to pH 5 but not soluble at the neutral and alkali ranges of a pH of higher than 5. Accordingly, a polymer usually used as a gastric-soluble polymer in this pharmaceutical field can be suitably used. Examples of the low pH-soluble polymer are, for instance, polyvinyl acetal diethylaminoacetate, methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer such as Eudragit E100 (trade name, commercially available from Röhm Pharma, Germany), polyvinyl aminoacetal and the like. These polymers soluble at low pH can be used alone or in admixture thereof. Among these, polyvinyl acetal diethylaminoacetate and methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer are preferable because these polymers are frequently used in the actual pharmaceutical production.

The enteric polymer used for the enteric coating film in the pharmaceutical preparation of the present invention can be a film-formable polymeric substance which is soluble in an aqueous medium of a pH of higher than 5 but not soluble in an aqueous medium of a pH of at most 5. The enteric polymer used in the present invention includes, for instance, a cellulose derivative, an acrylic copolymer, a maleic copolymer, a polyvinyl derivative, shellac and the like.

The examples of the cellulose derivative are, for instance, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, hydroxymethylethylcellulose phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate maleate, cellulose benzoate phthalate, cellulose propionate phthalate, methylcellulose phthalate, carboxymethylethylcellulose, ethylhydroxyethylcellulose phthalate and the like. Among them, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate and carboxymethylethylcellulose are preferable. Further, hydroxypropylmethylcellulose acetate succinate is more preferable.

The examples of the acrylic copolymer are, for instance, styrene-acrylic acid copolymer, methyl acrylate-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, butyl acrylate-styrene-acrylic acid copolymer, methacrylic acid-methyl methacrylate copolymer such as Eudragit L100, Eudragit S or Eudragit S100 (each being trade name,

commercially available from Röhm Pharma, Germany), methacrylic acid-ethyl acrylate copolymer such as Eudragit L100-55 (trade name, commercially available from Röhm Pharma, Germany), methyl acrylate-methacrylic acid-octyl acrylate copolymer, and the like. Among them, methacrylic acid-methyl methacrylate copolymer is preferable.

The examples of the maleic copolymer are, for instance, vinyl acetate-maleic acid anhydride copolymer, styrene-maleic acid anhydride copolymer, styrene-maleic acid monoester copolymer, vinyl methyl ether-maleic acid anhydride copolymer, ethylene-maleic acid anhydride copolymer, vinyl butyl ether-maleic acid anhydride copolymer, acrylonitrile-methyl acrylate-maleic acid anhydride copolymer, butyl acrylate-styrene-maleic acid anhydride copolymer and the like.

The examples of the polyvinyl derivative are, for instance, polyvinyl alcohol phthalate, polyvinyl acetal phthalate, polyvinyl butylate phthalate, polyvinyl acetoacetal phthalate and the like.

In the pharmaceutical preparation of the present invention, the above-mentioned enteric polymer may be used alone or in the combination of one or more kinds thereof.

Among the above-mentioned enteric polymers, the cellulose derivative and the acrylic copolymer are preferable. Particularly, the cellulose derivative is preferable.

The mechanism in the pharmaceutical preparation of the present invention is as follows: When a pharmaceutical preparation stays in the stomach, an enteric coating film protects the pharmaceutical preparation from dissolution. Successively when the preparation transits from the stomach to the upper part of the small intestine, the enteric coating film dissolves and starts to disappear. Then, the digestive juice gradually penetrates through a low pH-soluble polymer film and a hard capsule to enter the hard capsule, and thereby an acidic substance is dissolved. The solution having low pH which is produced by the dissolution of the acidic substance, dissolves the hard capsule and the low pH-soluble polymer film, resulting in disappearance thereof. At this time, the contents of the hard capsule are quickly released.

Accordingly, the pharmaceutical preparation of the present invention makes it possible for contents of a hard capsule to be selectively released at any desired site of the lower part of the digestive tract by controlling the amount of polymer(s) used for a low pH-soluble polymer film and by selecting the kind of a low pH-soluble polymer and an acidic substance.

The time period from the discharge of the pharmaceutical preparation from the stomach till contents of the hard capsule start to be released in the intestine (hereinafter referred to as "lag-time") can be determined by controlling the amount of polymer(s) used for a low pH-soluble polymer film and by selecting the kind of a low pH-soluble polymer and an acidic substance. For example, when the amount of polymer(s) used for a low pH-soluble polymer film is increased or decreased, the lag-time becomes long or short.

The general passage time of a pharmaceutical preparation through the small intestine is recognized to be  $3 \pm 1$  hours. Therefore, when the lag-time is adjusted to be about 2 hours, about 4 hours and about 7 hours, there can be obtained pharmaceutical preparations of the present invention from which the contents of the hard capsule would be released approximately at the lower part of the ileum, the ascending colon and the transverse colon, respectively. When the longer lag-time is determined, there can be obtained a pharmaceutical preparation from which the contents of the hard capsule would be released approximately at the lower part of the large intestine.

The pharmaceutical preparation of the present invention is suitably designed so that contents of a hard capsule cannot substantially be released during the length of time corresponding to the desired lag-time when the dissolution test is carried out with the JP 2nd-Fluid (JP XII) according to the dissolution test (paddle method) described in the 12th Japanese Pharmacopoeia (JP XII).

Each amount of the low pH-soluble polymer film and the enteric coating film is not particularly limited.

A suitable amount of the low pH-soluble polymer film varies with the length of the predetermined lag-time and the combination of the components. A suitable amount of the enteric coating film may be an amount in the extent that the contents of a hard capsule are not released in the stomach. These amounts can easily be determined by carrying out the dissolution test. In general, it is preferable that the amount of the low pH-soluble polymer film is determined to be from 5 to 500 % by weight and the amount of the enteric coating film is determined to be from 10 to 400 % by weight, based on the weight of the hard capsule itself (empty capsule).

As the combination of each polymer of the low pH-soluble polymer film and the enteric coating film in the present invention, the low pH-soluble polymers and the enteric polymers as mentioned above are selected and used with taking into account the predetermined lag-time, the properties of the hard capsule, the kind of the acidic substance and the like.

Examples of preferable combinations of each polymer of the low pH-soluble polymer film and the enteric coating film in the present invention are shown in Table 1, and examples of preferable combinations of each concrete polymer thereof in Table 2.

Table 1

No.	Polymer of the low pH-soluble polymer film	Polymer of the enteric coating film
1	Polyvinyl acetal diethylaminoacetate	Enteric cellulose derivative
2	Polyvinyl acetal diethylaminoacetate	Shellac
3	Polyvinyl acetal diethylaminoacetate	Enteric acrylic copolymer
4	Polyvinyl acetal diethylaminoacetate	Enteric maleic copolymer
5	Polyvinyl acetal diethylaminoacetate	Enteric polyvinyl derivative
6	Methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer	Enteric cellulose derivative
7	Methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer	Shellac
8	Methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer	Enteric acrylic copolymer
9	Methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer	Enteric maleic copolymer
10	Methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer	Enteric polyvinyl delivative

Table 2

No.	Polymer of the low pH-soluble polymer film	Polymer of the enteric coating film
11	Polyvinyl acetal diethylaminoacetate	Hydroxypropylmethylcellulose acetate succinate
12	Polyvinyl acetal diethylaminoacetate	Hydroxypropylmethylcellulose phthalate
13	Polyvinyl acetal diethylaminoacetate	Carboxymethylethylcellulose
14	Polyvinyl acetal diethylaminoacetate	Methacrylic acid-methyl methacrylate copolymer
15	Methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer	Hydroxypropylmethylcellulose acetate succinate
16	Methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer	Hydroxypropylmethylcellulose phthalate
17	Methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer	Carboxymethylethylcellulose
18	Methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer	Methacrylic acid-methyl methacrylate copolymer

A medicament, a pharmaceutical preparation, a functional substance or the like may be contained in the hard capsule in the pharmaceutical preparation of the present invention.

The medicament to be contained in the hard capsule is not particularly limited as long as it is orally administerable. Examples of such medicaments are, for instance, chemotherapeutic agents, antibiotics, respiratory stimulants, antitussives, expectorants, antimalignantumor agents, autonomic agents, psychotropic agents, local anesthetics, muscle relaxants, agents affecting the digestive organs, antihistamines, toxicopetic agents, hypnotics, sedatives, antiepileptics, antipyretics, analgesics, antiinflammatory agents, cardiotonics, antiarrhythmic agents, diuretics, vasodilators, antileptic agents, nutrients, tonics, alteratives, anticoagulants, agents for liver disease, hypoglycemics, antihypertensives and the like.

Particularly, it is beneficial to use a medicament which locally acts on the large intestine, a medicament which is desired to be absorbed at the large intestine for the reason that the medicament is quickly degraded at the small intestine, and the like.

The pharmaceutical preparation to be contained in the hard capsule is not particularly limited as long as it is orally administerable. Examples of such pharmaceutical preparations are, for instance, powder, fine granule, granule, tablet, oily suspensions and the like. These pharmaceutical preparations may have a controlled release property such as sustained release property.

The functional substance to be contained in the hard capsule is a substance which has no pharmacological action but exerts a favorable influence *in vivo*. Examples of the functional substance are, for instance, useful enterobacterium like lactobacillus, calcium polycarbophil which swells in the large intestine to facilitate the defecation, and the like. The functional substance may not be a single substance. For example, to the above-mentioned calcium polycarbophil, there can be added e.g. cellulose, a sodium carboxymethyl starch such as Exprotab (trade name, commercially available from Kimura Sangyo Co., Ltd., Japan), a pretreated starch such as Starch 1500 (trade name, commercially available from Japan Colorcon Ltd., Japan) and the like.

In the case that a medicament and an acidic substance are contained in a hard capsule, the medicament is filled into the capsule in the state that the chemical stability of the medicament and the acidic substance can be assured during storage for a long period. The form of both components and the method for filling them etc. are not particularly limited. For instance, after mixing a medicament and an acidic substance in the form of crystal or powder as it is, the resulting mixture may be filled into a hard capsule, or the resulting mixture may be granulated and the granule is formed into powder, fine granule, granule or tablet and filled into a hard capsule. Alternatively, for the purpose of avoiding interaction between a medicament and an acidic substance, each material in the form of crystal or powder may be separately layered using a partition layer to prevent direct contact of both materials and, after preparing tablets of a medicament and an acidic substance separately, the tablets may be filled into a hard capsule. As to the partition, any substance which does not cause an unfavorable effect on the pharmaceutical preparation of the present invention can be used for the material of the partition, and, for instance, an excipient etc. which are usually used in this field can be used.

In the case that a functional substance is contained in a hard capsule, the filling of the functional substance can be carried out in the same way as in the case of a medicament.

In the pharmaceutical preparation of the present invention, an intermediate layer comprising at least one member selected from the group consisting of a medicament and a water-soluble substance can be provided between the low pH-soluble polymer film and the enteric coating film, if desired.

Providing an intermediate layer comprising a water-soluble substance may make it possible to prevent the possible alteration of the characteristic of the low pH-soluble polymer film which occurs in forming the enteric coating film. The medicament contained in the intermediate layer may be the same or different from a medicament which can be contained in the hard capsule.

Examples of the medicament usable for the intermediate layer are not particularly limited as long as it is an orally administrable medicament as cited above. Examples of the water-soluble substance usable for the intermediate layer are, for instance, a water-soluble polymeric substance, e.g. a water-soluble polysaccharide ether such as methylcellulose, hydroxypropylcellulose or hydroxypropylmethylcellulose (for example, TC-5 (trade name, commercially available from Shin-Etsu Chemical Co., Ltd.)), a water-soluble polyvinyl derivative such as polyvinylpyrrolidone or polyvinylalcohol, a polysaccharide such as pullulan, a polyethyleneglycol etc.; a saccharide, e.g. a monosaccharide such as glucose, a disaccharide such as sucrose etc.; a low molecular electrolyte, e.g. an inorganic salt such as sodium chloride etc.; and the like.

It is preferable that the amount of the intermediate layer is determined to be from 8 to 320 % by weight, in particular, from 16 to 80 % by weight, based on the weight of the hard capsule itself (empty capsule).

The method for preparing the pharmaceutical preparation of the present invention is not particularly limited and the general method known to a person skilled in the art can be used. The form of the acidic substance and contents of the hard capsule may be crystal, powder, fine granule, granule, tablet and the like. For example, a hard capsule containing a medicament can be prepared by mixing an acidic substance and a medicament together with an excipient,



a binder, a lubricant and the like and by preparing a granule from the resulting mixture according to the general method such as wet granulation or dry granulation and then by filling the granule into a hard capsule.

The coating of the low pH-soluble polymer film, the enteric coating film and an intermediate layer between the low pH-soluble polymer film and the enteric coating film can be carried out according to the method usually used in this field by means of HICOATER (trade name, made by Freund Industrial Co., Ltd., Tokyo, Japan), a pan coating apparatus, a centrifugal fluidizing type granulating and coating apparatus or the like. Both aqueous coating methods and non-aqueous coating methods generally used in this field can be employed for the above-mentioned coating.

As to a coating solution, examples of the solvent used for the coating solution are, for instance, an alcohol such as methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, 2-methoxyethanol (trade name: Methyl cellosolve, commercially available from KATAYAMA CHEMICAL INDUSTRIES CO., LTD., Japan) or 2-ethoxyethanol (trade name: Cellosolve, commercially available from KATAYAMA CHEMICAL INDUSTRIES CO., LTD., Japan); a hydrocarbon such as hexane, cyclohexane, petroleum ether, petroleum benzine, ligroin, benzene, toluene or xylene; a ketone such as acetone or methyl ethyl ketone; a hydrocarbon halide such as dichloromethane, chloroform, carbon tetrachloride, ethylene dichloride, trichloroethylene or 1,1,1-trichloroethane; an ester such as methyl acetate, ethyl acetate or butyl acetate; an ether such as isopropyl ether or dioxane; water, and the like.

Among the above-mentioned solvents, a solvent to be used can be selected according to a property of each coating layer and can suitably be used in admixture thereof. Among these examples, particularly an alcohol, a hydrocarbon halide, a ketone, water and the like are preferable, and concretely ethyl alcohol, acetone, water and the like are preferable.

In the pharmaceutical preparation of the present invention, a sealing means can be provided around a joint of a body and a cap of the hard capsule. By providing a sealing means, there can be obtained an excellent pharmaceutical preparation which has a little variation of the lag-time between each pharmaceutical preparation.

A sealing agent used for the sealing means can be a substance which can make the surface of the hard capsule at the joint of a body and a cap smooth. Examples of the sealing agent are, for instance, a water-soluble polymer, an water-insoluble polymer, a low pH-soluble polymer, an enteric polymer, a saccharide, a low molecular electrolyte and the like.

As the water-soluble polymer used as the sealing agent, there can be used water-soluble polymers which can be used for the intermediate layer. Examples of the water-soluble polymer are, for instance, a water-soluble polysaccharide ether such as methylcellulose, hydroxypropylcellulose or hydroxypropylmethylcellulose; a water-soluble polyvinyl derivative such as polyvinylpyrrolidone or polyvinylalcohol; a polysaccharide such as pullulan; a polyethyleneglycol; and the like.

Examples of the water-insoluble polymer used as the sealing agent are, for instance, a water-insoluble acrylic copolymer, e.g. ethyl acrylate-methyl methacrylate-trimethylammoniummethyl methacrylate chloride copolymer such as Eudragit RS or Eudragit RL (each being trade name, commercially available from Röhm Pharma, Germany), ethyl acrylate-methyl methacrylate copolymer such as Eudragit NE (trade name, commercially available from Röhm Pharma, Germany) and the like; a water-insoluble cellulose derivative such as ethylcellulose or cellulose acetate; a water-insoluble polyvinyl derivative such as polyvinyl acetate or polyvinyl chloride; and a mixture thereof.

As the low pH-soluble polymer used as the sealing agent, there can be used polymers soluble at low pH which can be used in the low pH-soluble polymer film in the present invention, for instance, polyvinylacetal diethylaminoacetate and the like.

As the enteric polymer used as the sealing agent, there can be used enteric polymers which can be used in the enteric coating film in the present invention, for instance, hydroxypropylmethylcellulose acetate succinate, methacrylic acid-methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer and the like.

As the saccharide and the low molecular electrolyte used as the sealing agent, there can be used saccharides and low molecular electrolytes which can be used for the intermediate layer. Examples of the saccharide are, for instance, a monosaccharide such as glucose, a disaccharide such as sucrose, and the like, and examples of the low molecular electrolyte are, for instance, an inorganic salt such as sodium chloride, and the like.

The above-mentioned sealing agent can be used alone or in admixture thereof.

The sealing means can be provided by applying a solution obtained by dissolving the sealing agent in a solvent on the joint, using a capsule sealing machine such as The Mod. SL/M (trade name, made by MG 2 S.p.A., Italy) or HICAPSEAL 15 (trade name, made by Japan Elanco Co., Ltd., Japan) or using e.g. a pipet such as a Pasteur pipet and by drying, to seal the joint. The coating amount of the sealing means is from 0.16 to 16 % by weight, preferably from 0.8 to 3.2 % by weight, based on the weight of the hard capsule itself (empty capsule).

Examples of the solvent are the same as those of the coating solutions usable for the coating of the low pH-soluble polymer film, etc.

To each of the contents of the hard capsule, the sealing means, the low pH-soluble polymer film, the enteric coating film and the intermediate layer between the low pH-soluble polymer film and the enteric coating film, if necessary, there can be added various additives generally used in the art of pharmaceutical preparation, for instance, an excipient, a

binder, a disintegrant, a lubricant, an aggregation-preventing agent, a coating auxiliary, a coloring agent, a masking agent, a plasticizer to improve the coating property and the film-formability etc., a surfactant, an antistatic agent, an additive for controlling transmittance of light, and the like.

Examples of the excipient are, for instance, a saccharide such as sucrose, lactose, mannitol or glucose, starch, partially pregelatinized starch, crystalline cellulose, calcium phosphate, calcium sulfate, precipitated calcium carbonate, hydrated silicon dioxide and the like.

Examples of the binder are, for instance, an oligosaccharide or sugar alcohol such as sucrose, glucose, lactose, maltose, sorbitol or mannitol; a polysaccharide such as dextrin, starch, sodium alginate, carrageenan, guar gum, arabic gum or agar; a natural high molecular substance such as tragacanth, gelatin or gluten; a cellulose derivative such as methylcellulose, ethylcellulose, sodium carboxymethylcellulose or hydroxypropylmethylcellulose; a synthetic polymer such as polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, polyethyleneglycol, polyacrylic acid or polymethacrylic acid; and the like.

Examples of the disintegrant are, for instance, calcium carboxymethylcellulose, sodium carboxymethylstarch, corn starch, hydroxypropylstarch, partially pregelatinized starch, low-substituted hydroxypropylcellulose, polyvinylpyrrolidone, calcium cross-linked carboxymethylcellulose and the like.

Examples of the lubricant and the aggregation-preventing agent are, for instance, talc, magnesium stearate, calcium stearate, colloidal silicon dioxide, stearic acid, hydrated silicon dioxide, synthetic magnesium silicate, fine grain silicon oxide, starch, sodium lauryl sulfate, boric acid, magnesium oxide, a wax, a hydrogenated oil, a polyethyleneglycol, sodium benzoate and the like.

Examples of the coating auxiliary are, for instance, a hydrogenated oil such as K-3 WAX (trade name, commercially available from Kawaken Fine Chemicals Co., Ltd., Japan), stearic acid such as NAA-174 (trade name, commercially available from NOF Corporation, Japan), calcium stearate, a polyoxyl stearate such as NONION S-154 (trade name, commercially available from MATSUMOTO TRADING CO., LTD., Japan), magnesium stearate, cetanol such as NAA-44 (trade name, commercially available from NOF Corporation) and the like.

Examples of the coloring agent are, for instance, a food color, a lake, caramel, a carotene, an annatto, cochineal, iron sesquioxide, an opaque coloring agent OPALUX mainly made of a lake and syrup, and the like.

Concrete examples thereof are, for instance, a food color such as Food Red No. 2, Food Red No. 3, Food Yellow No. 4, Food Yellow No. 5, Food Green No. 3, Food Blue No. 1, Food Blue No. 2 or Food Purple No. 1, a food aluminum lake such as Food Red No. 2 aluminum lake, Food Red No. 3 aluminum lake, Food Yellow No. 4 aluminum lake, Food Yellow No. 5 aluminum lake, Food Green No. 3 aluminum lake, Food Blue No. 1 aluminum lake, Food Blue No. 2 aluminum lake or Food Purple No. 1 aluminum lake, an annatto (a natural color derived from *Bixa orellana* L.), carmine (aluminum carminate), a Pearl essence (the principal ingredient thereof is guanine) and the like.

Examples of the masking agent are, for instance, titanium dioxide, precipitated calcium carbonate, calcium secondary phosphate, calcium sulfate and the like.

Examples of the plasticizer are, for instance, a phthalic acid derivative such as diethyl phthalate, dibutyl phthalate or butyl phthalyl butyl glycolate, a silicone oil, triacetin, propylene glycol, a polyethyleneglycol and the like.

Examples of the surfactant are, for instance, a nonionic surfactant such as sorbitan sesquioleate, polyoxyethylene sorbitan monooleate, polyoxyethylene monostearate, glycerol monostearate, propylene glycol monolaurate, polyoxyethylene lauryl ether, polyoxyethylene cetyl ether or polyoxyethylene hydrogenated castor oil; an ionic surfactant such as sodium dodecyl sulfate or benzalkonium chloride; and the like.

Examples of the antistatic agent are, for instance, hydrated silicon dioxide, silicic acid and the like.

Examples of the additive for controlling transmittance of light are, for instance, titanium oxide, talc and the like.

These additives can be added in any amount and at any time within the scope of the knowledge usually used in the field of pharmaceutical preparation.

As to the pharmaceutical preparation of the present invention, typical ones are shown in Figs. 1 to 3.

In the pharmaceutical preparation of the present invention shown in Fig. 1, an acidic substance and, if desired, a medicament, a pharmaceutical preparation or a functional substance, 1 are contained in a hard capsule and the hard capsule is firstly coated with a low pH-soluble polymer film 4 and further coated with an enteric coating film 5.

In the pharmaceutical preparation of the present invention shown in Fig. 2, a sealing means 6 is provided around the joint 8 of the body 3 and the cap 2 in the hard capsule in the pharmaceutical preparation in Fig. 1. The joint 8 means a boundary of a connecting portion of the body 3 and the cap 2 of the hard capsule.

In the pharmaceutical preparation of the present invention shown in Fig. 3, a sealing means 6 is provided around the joint 8 in the hard capsule and an intermediate layer 7 comprising a medicament and/or a water-soluble substance is provided between the low pH-soluble polymer film 4 and the enteric coating film 5 in the pharmaceutical preparation in Fig. 1.

Fig. 4 shows a perspective view of a hard capsule with a sealing means around the joint 8 of the body 3 and the cap 2 thereof.

Preferred embodiments of the pharmaceutical preparation of the present invention are given below.

(1) The kind of and the amount of polymer(s) used for the low pH-soluble polymer film and the kind of the acidic substance are selected so that contents of a hard capsule can be released at any desired site of the lower part of the digestive tract;

(2) The kind of and the amount of polymer(s) used for the low pH-soluble polymer film and the kind of the acidic substance are selected so that contents of a hard capsule can be released at any desired site between the jejunum and the rectum;

(3) The kind of and the amount of polymer(s) used for the low pH-soluble polymer film and the kind of the acidic substance are selected so that contents of a hard capsule can be released at any desired site between the ileum and the rectum;

(4) The kind of and the amount of polymer(s) used for the low pH-soluble polymer film and the kind of the acidic substance are selected so that contents of a hard capsule can be released at any desired site of the large intestine;

(5) The kinds of and the amount of polymer(s) used for the low pH-soluble polymer film and the kind of the acidic substance are determined so that contents of a hard capsule can be released after the desired time period when a dissolution test is carried out with the JP 2nd-Fluid according to the disintegration test described in JP XII;

(6) The acidic substance is an organic acid;

(7) The acidic substance is at least one member selected from the group consisting of succinic acid, maleic acid, tartaric acid, citric acid, fumaric acid and malic acid;

(8) The hard capsule is commercially available;

(9) The hard capsule is a gelatin capsule, a corn starch capsule or a hydroxypropylmethylcellulose capsule;

(10) The hard capsule is a gelatin capsule or a hydroxypropylmethylcellulose capsule;

(11) The hard capsule is a gelatin capsule;

(12) The low pH-soluble polymer film comprises a film-formable polymeric substance which is soluble at an acidic range of from pH 1 to pH 5 but not soluble at a neutral and alkaline range of a pH of higher than 5;

(13) The low pH-soluble polymer film comprises at least one member selected from the group consisting of polyvinylacetal diethylaminoacetate and methyl methacrylate-butyl methacrylate-dimethyl methacrylate copolymer;

(14) The enteric coating film comprises a film-formable polymeric substance which is soluble in an aqueous medium having a pH of higher than 5 but not soluble in an aqueous medium of a pH of at most 5;

(15) The enteric coating film comprises at least one member selected from the group consisting of a cellulose derivative, shellac, an acrylic copolymer, a maleic copolymer and a polyvinyl derivative; and

(16) The enteric coating film comprises at least one member selected from the group consisting of hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, carboxymethylcellulose and methacrylic acid-methyl methacrylate copolymer;

The present invention is more specifically described and explained by means of the following Examples and Experimental Examples.

#### Experimental Example 1

##### (1) Dissolution Test

With respect to the pharmaceutical preparation containing prednisolone obtained in the following Example 1, a dissolution test was carried out with the JP 1st-Fluid of the disintegration test in JP XII (pH 1.2, hereinafter referred to as the JP 1st-Fluid) and the JP 2nd-Fluid of the disintegration test in JP XII (pH 6.8, hereinafter referred to as the JP 2nd-Fluid), using 900 mL of the dissolution fluid at 37°C and at the rotation speed of 100 rpm according to the paddle method based on the specification of the dissolution test described in JP XII.

The results of the dissolution test are shown in Fig. 5. With respect to the pharmaceutical preparation of the present invention, the medicament was not dissolved at all for a long time in the JP 1st-Fluid, which means that the acid resistance of the pharmaceutical preparation was maintained sufficiently.

In the JP 2nd-Fluid, the medicament was quickly dissolved after the lag-time of about 4 hours and it is seen that it takes about 1 hour after the start of dissolution to dissolve 80 % of the medicament.

##### (2) in vivo Absorption Test

In the course of preparing the above-mentioned pharmaceutical preparation, an intermediate layer was provided between the Eudragit E100 layer and the hydroxypropylmethylcellulose acetate succinate layer by coating the Eudragit E100 layer with theophylline as an indicator of gastric emptying in a coating amount of 20 mg per capsule. Thus a pharmaceutical preparation having an intermediate layer in the pharmaceutical preparation of the Experimental Example 1(1) was obtained.